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Risk of Altitude Exposure in Sickle Cell Disease

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The risk of altitude-induced hypoxemia causing painful crisis was determined in a group of 45 predominantly adult patients with sickle cell disease. The patients were divided into two groups: those with hemoglobin (Hb) SS and those with Hb SC or Hb S β-thalassemia. Altitude exposures were divided into airplane travel and mountain visits, and the latter subdivided into stays at 4,400 or 6,320 ft. The average risk of crisis was higher for both groups while in the mountains (37.9 percent and 56.6 percent, respectively) than it was during airplane travel (10.8 percent and 13.5 percent, respectively). The latter group had more splenic crises than the former group and also had a greater risk at 6,320 ft (65.9 percent) than at 4,400 ft (20.0 percent). Patients with sickle cell disease are at high risk of crisis in the mountains, and we advise those with intact spleens to breathe supplemental oxygen during air travel.

IT IS WELL ESTABLISHED that manifestations of sickle cell disease are exacerbated by hypoxemia.[1] Several case reports indicate that not only these patients but those with only sickle trait are thought to be at increased risk during airplane travel[2,3] and while in the mountains.[4-6]

A group of pediatric and adult patients with sickle cell disease was reported to have a 20 percent to 30 percent incidence of a crisis with exposure to travel in the mountains or in pressurized aircraft.[7] Those in that study, however, were already acclimatized to altitude by virtue of residing at an elevation of 5,000 ft above sea level; thus, their experience may not accurately reflect the risk of most patients with sickle cell disease. We studied a largely adult population of patients with sickle cell disease who reside near sea level in San Francisco; the results are reported herein.

Patients and Methods

We studied retrospectively 45 patients with sickle cell disease who had a history of high altitude exposure. Of these, 38 were followed up at the San Francisco General Hospital Hematology Clinic and 7 were followed up at other centers in San Francisco. Twenty-six patients were homozygous for hemoglobin (Hb) S, 13 were doubly heterozygous for Hb S and Hb C, and 6 were doubly heterozygous for Hb S and β-thalassemia. Hb A, Hb S and Hb C concentrations were deter-

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TABLE 1.—*The Risk of Splenic, Nonsplenic and Total Painful Crises During Mountain and Air Travel in Patients With Sickle Cell Disease*

Group	Painful Events/Patient			Painful Events/Times at Risk			Average Risk	
	Splenic Crisis	Nonsplenic Crisis	Total	Splenic Crisis	Nonsplenic Crisis	Total	Nonsplenic Crisis (percent)	Total (percent)
Mountain exposure								
Hb SS	0/12 (0.0%)	6/12 (50.0%)	6/12 (50.0%)	0/35 (0.0%)	6/35 (17.1%)	6/35 (17.1%)	37.9	37.9
Hb SC/Hb S β-thal	4/14 (28.6%)	5/14 (35.7%)	9/14 (64.3%)	4/59 (6.8%)	18/59 (30.5%)	22/59 (37.3%)	28.1	56.6
Air travel								
Hb SS	1/23 (4.3%)	2/23 (8.7%)	3/23 (13.0%)	1/221 (0.5%)	2/221 (0.9%)	3/221 (1.4%)	6.5	10.8
Hb SC/Hb S β-thal	4/17 (23.5%)	2/17 (11.8%)	6/17 (35.3%)	4/443 (0.9%)	23/443 (5.2%)	27/443 (6.1%)	5.5	13.5

β-thal = β-thalassemia

mined by hemoglobin electrophoresis; concentration of Hb A_2 was determined by column chromatography,[8,9] Hb F concentration was determined by alkaline denaturation.[10] Erythrocyte indices were determined by the Coulter Model S. The patients ranged in age from 10 to 62 years, with only five under the age of 18—two with Hb SC and three with Hb SS. The youngest patient with Hb SS was ten years old. All patients lived near sea level in San Francisco.

Because of the vulnerability of the spleen to infarctive crisis, the patients were divided into two groups: those with Hb SS, who generally, as adults, have splenic atrophy,[11] and those with Hb SC or Hb S β-thalassemia, who generally have normal-sized or enlarged spleens. Altitude exposures were divided into airplane travel and visits to the mountains, during which no strenuous physical exertion such as mountain climbing was undertaken. With the exception of one flight by a patient with Hb SS in an unpressurized aircraft, all flights were in commercial pressurized planes. Air travel time varied from 1 to 6 hours, except for one international flight of 14 hours.

One of us (M.G.) asked each patient to recall the total number of mountain or airplane experiences and the number that resulted in painful episodes. An altitude-related painful crisis was defined as moderate to severe pain in the extremities, back, chest or abdomen that occurred during or immediately after exposure to high altitude. We did not require hospital admittance or physician verification of a painful episode but relied on the patients' recollections. Left upper quadrant abdominal pain as the primary symptom complex was considered to be a probable splenic crisis. Nonspecific symptoms such as dizziness and headache were not considered to be altitude-related events. To assess the risk of hypoxemia in a more quantitative manner, we compared the risk of crisis in patients whose mountain visits were to Reno, Nevada, (elevation 4,400 ft) with those whose visits were to Lake Tahoe, Nevada, (elevation 6,320 ft). None of the crises reported to occur in the mountains occurred while patients were in transit over higher mountain passages to these areas—all occurred while patients were in Reno or at Lake Tahoe.

We assessed the information in three ways. First, we determined the fraction of patients who had a positive history of crisis with altitude exposure. Second, we determined the fraction of total times at risk that resulted in a crisis. Finally, because both of the above determinations may be skewed by patients with unusually severe or unusually mild clinical courses, we calculated the average risk per patient by determining for each patient the number of crises per times at risk, determining the sum of these fractions from all of the patients in each group, and dividing this sum by the number of patients in each group:

$$\text{Average risk} = \frac{\Sigma\left(\frac{\text{crises}_1}{\text{exposures}_1}\right) + \left(\frac{\text{crises}_2}{\text{exposures}_2}\right) \cdots + \left(\frac{\text{crises}_n}{\text{exposures}_n}\right)}{n}$$

Results

Results of analyses of painful crises occurring during mountain travel are shown in Table 1. In 50 percent of the patients with Hb SS and in 64.3 percent of the patients with Hb SC disease or Hb S β-thalassemia, painful crises occurred during travel in the mountains. When the occurrence of painful crises during mountain travel was

assessed in terms of the total number of times at risk, both groups had a lower frequency of crises, a finding that reflects that patients who had had a crisis during initial mountain travel tended to avoid further exposure. Of the exposures, 17.1 percent resulted in painful crises for the Hb SS group and 37.3 percent for the Hb SC disease and Hb S β-thalassemia group. The average risk of crisis per patient was 37.9 percent for Hb SS and 56.6 percent for patients with Hb SC disease or Hb β-thalassemia.

The analysis of painful crises occurring during airplane travel are also shown in Table 1. In 13 percent of the patients with Hb SS and in 35.3 percent of the patients with Hb SC or Hb S β-thalassemia, painful crises occurred during airplane travel. The percent of the exposures that resulted in painful crises were 1.4 percent in the former group and 6.1 percent in the latter group. Again, these lower frequencies reflect a tendency to avoid further exposure after an initial painful crisis. The average risk of crisis per patient was 10.8 percent for the Hb SS group and 13.5 percent for the Hb SC and Hb S β-thalassemia group.

No splenic crisis occurred during mountain exposure in those with Hb SS, but crisis occurred in 28.6 percent of those with Hb SC or Hb S β-thalassemia and in 6.8 percent of their exposures. During air travel 4.3 percent of patients with Hb SS (0.5 percent of their flights) had a splenic crisis. Splenic crisis occurred in 23.5 percent of patients with Hb SC or Hb S β-thalassemia (0.9 percent of their flights).

Subtracting the number of splenic crises from the total number of painful episodes showed that the risk of nonsplenic crisis is similar in both groups for both types of hypoxic exposures (Table 1). During air travel nonsplenic crises ocurred in 8.7 percent of the Hb SS patients and in 0.9 percent of their flights; their average risk of nonsplenic crisis was 6.5 percent. Air travel resulted in nonsplenic crises in 11.8 percent of the Hb SC or Hb S β-thalassemia patients and in 5.2 percent of their flights; their average risk of nonsplenic crisis was 5.5 percent. During mountain exposure nonsplenic crises occurred in 50 percent of those with Hb SS and in 17.1 percent of their visits, and their average risk of nonsplenic crisis was 37.9 percent. Mountain exposure resulted in nonsplenic crises in 35.7 percent of those with Hb SC or Hb S β-thalassemia and in 30.5 percent of their mountain visits, and their average risk of nonsplenic crisis was 28.1 percent.

TABLE 2.—*The Risk of Painful Crisis in Patients With Sickle Cell Disease During Mountain Exposure at Lake Tahoe (6,320 ft) and in Reno (4,400 ft)*

Exposure Site	Events/ Patient	Events/ Times at Risk	Average Risk (percent)
Exposure of SS group to different altitudes			
Lake Tahoe ..	3/5 (60.0%)	3/25 (12.0%)	31.0
Reno	3/7 (42.9%)	3/10 (30.0%)	42.9
Exposure of the SC/S β-thalassemia group to different altitudes			
Lake Tahoe ..	7/9 (77.8%)	20/32 (62.5%)	65.9
Reno	2/5 (40.0%)	2/27 (7.4%)	20.0

Results of a comparison between events at Lake Tahoe and in Reno are shown in Table 2. Of the patients with Hb SS, 60 percent had a crisis while at 6,320 ft and 42.9 percent had a crisis at 4,400 ft. The percentage of events per times at risk was 12 percent at Lake Tahoe and 30 percent in Reno. Their average risk of having a crisis was 31 percent at 6,320 ft and 42.9 percent at 4,400 ft. Of the patients with Hb SC or Hb S β-thalassemia, 77.8 had a crisis at 6,320 ft and 40 percent had a crisis at 4,400 ft. The percentage of events per times at risk was 62.5 percent at Lake Tahoe and 7.4 percent in Reno. Their average risk of having a crisis was 65.9 percent at 6,320 ft and 20 percent at 4,400 ft.

Discussion

In our study, mountain travel presented substantial risk of a painful crisis to both groups of patients. And, while airplane travel resulted in few painful crises in patients with Hb SS, those with Hb SC or Hb S β-thalassemia (especially those with splenomegaly) had substantial risk of a painful crisis (although less than during mountain travel).

Ascent to mountain elevations or travel in commercial pressurized planes that maintain cabin pressure at 5,000 to 7,000 feet[2] is associated with a drop in oxygen pressure (Po_2) that may adversely affect patients with Hb S. Another risk of altitude is its effect on Hb-oxygen affinity. In nonsickle subjects the initial increase in affinity caused by respiratory alkalosis[1] is followed in 12 hours by an overall decrease in affinity due to elevations of 2,3-diphosphoglycerate levels.[12,13] If such a course occurs in sickle patients, who have baseline elevations in 2,3-diphosphoglycerate levels,[14,15] it could explain the higher incidence of

crisis during the longer exposure of mountain visits, as compared with airplane flights. This may also be the explanation for why the only flight that lasted longer than 12 hours resulted in a crisis in the patient.

Our comparison of mountain travel locations indicated no consistent difference between risks at Lake Tahoe and in Reno for Hb SS patients. However, there was a much higher incidence of painful events at 6,320 ft than at 4,400 ft for patients with Hb SC or Hb S β-thalassemia.

Only patients with an intact spleen had symptoms consistent with splenic crisis at high altitude. Although it has been suggested that splenic crisis during airplane travel may be related to inactivity and the wearing of seatbelts,[2,3] in our survey splenic crisis ocurred more frequently during mountain exposure (4/94 or 4.3 percent) than during airplane flight (5/664 or 0.75 percent). Most of the patients in whom splenic crisis developed had Hb SC or Hb S β-thalassemia, and all had enlarged spleens. There were, however, three patients in our study with splenomegaly who did not have any splenic pain during either airplane or mountain exposure. The only splenic crisis occurring among patients with Hb SS occurred after a 14-hour airplane flight in a Saudi Arabian patient with splenomegaly and an Hb F level of 26 percent. The fact that splenic infarction during air travel appears to be a previously unreported event in adults with Hb SS is attributable to the presence of autoinfarcted spleens in most such patients.[15]

The experiences of our patients during altitude exposure were remarkably variable. All those who had a splenic crisis did so only once, and none repeated that exposure. One patient with Hb SC had a splenectomy after a splenic crisis while in flight and has since flown without problems. Another patient with Hb SC had a splenic crisis during his only trip to the mountains after 150 airplane flights without incident. One patient with Hb SS had flown 70 times but had a painful crisis only in the mountains. A small number of patients made repeated trips to the mountains or took flights despite a painful crisis with virtually every exposure, but most patients who had problems at high altitude subsequently avoided such exposure. This tendency to avoid the cause of previous crises was responsible for the difference between the crisis per total exposure ratio and the crisis per patient ratio. Both of these estimates of risk can be skewed by patients whose individual risk at high altitude is unusually severe or unusually mild. To avoid this bias, we calculated the average risk per patient: the average risk was higher in the Hb SC or Hb S β-thalassemia group and seemed to reflect the greater incidence of intact spleens and associated splenic crises in this group. This was corroborated by a similar incidence of crisis for this and the Hb SS group when the number of splenic events was subtracted from both.

Patients from Denver with sickle cell disease have been shown to have a similar risk of crisis during both air travel and mountain exposure.[7] Our study not only confirms this risk, but also, paradoxically, shows an even higher incidence of risk for patients who live at sea level and who, presumably, have lower levels of 2,3-diphosphoglycerate. The reason why living at high altitude should create a protective effect is not clear.

Conclusion

To diminish the risk of crisis, patients with sickle cell disease should be advised to remain well hydrated during hypoxic exposure. Based on our data, all patients with sickle cell disease who have had no previous mountain exposure should be advised to avoid the mountains, and patients with Hb SC or Hb S β-thalassemia who have splenomegaly should arrange in advance for in-flight oxygen. We believe that adult patients with Hb SS do not need supplemental oxygen unless they are among the 6 percent[11] of adult patients with Hb SS and intact spleens.

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